

I. Background and Goals

The Multiethnic Study of Atherosclerosis (MESA) is studying risk factors and measures of cardiovascular disease that relate to progression of subclinical to clinical disease. An integral part of this study is the measurement of coronary artery calcium using either electron beam computed tomography (EBCT) or helical computed tomography (HCT). Coronary calcium will be assessed in relation to the risk of future cardiac events, and from repeated scans in selected individuals, the progression of coronary calcium will be related to baseline risk factors and risk of future events.

Separate training sessions will be held in March 2000 in Los Angeles (for the EBCT centers) and in Wake Forest (for the Helical CT centers) for all technicians participating in the MESA study. A pilot feasibility study will take place in May 2000 on a selected sample of volunteers (10 from each Field Center). Approximately 6,500 participants will be scanned among the 6 centers during the initial (2-year) examination occurring between July 2000 and June 2002. A sample of about half of participants will receive repeated scans during three subsequent, follow-up examinations in future years.

Goals:

- 1) To examine the relation of baseline measures of coronary calcium quantity (score and volume measures) to future risk of cardiac events
- 2) To examine the relation of baseline measures of coronary calcium to other risk factors and measures of subclinical disease (e.g., MRI and ultrasound measures).
- 3) To examine the relation of progression of coronary calcium to the risk of future cardiac events, as well as to risk factors at baseline and progression of risk factors.
- 4) To examine the above goals by ethnic and gender strata, when possible.

II. Qualifications of Personnel

Each Field Center has a designated physician to oversee the general performance of CT examination. A reading center investigator will provide the necessary on-site training.

Field Center technologists should have appropriate knowledge of cross-sectional anatomy, physiology, and pathology related to the heart. Technologists must be certified as RTs in their state. It is recommended that technologists also have at least two years of experience in chest computed tomography. The technologist should also have a basic knowledge of cardiac CT, knowledge of computer software applications, data formatting, and experience with the workstations and data formatting / transmission procedures used.

Each technologist involved in the study should also have a complete understanding of this protocol, be experienced at providing breath-holding instruction, ECG gating, operation of the EBCT or HCT equipment. To ensure quality control, each Field Center should have designated CT technicians who will perform the MESA examinations, once appropriate training, including the March 2000 training course, has been provided.

III. Scanning Equipment and Centers

The scanners used will be:

Imatron C-150:	Saint Francis Hospital; Roslyn, New York
Imatron C-150	Northwestern University, Chicago, Illinois
Imatron C-150	UCLA School of Medicine, Los Angeles, CA
General Electric LightSpeed :	Wake Forest Bowman Grey School of Medicine
Siemens S4+ Volume Zoom:	Johns Hopkins Univ. Medical Center, Baltimore
Siemens S4+ Volume Zoom:	Univ of Minnesota Medical Center, Minneapolis

Each center will be responsible for scanning approximately one sixth of the cohort of 6500 individuals. For purposes of increased reliability and quality control, each subject will be scanned twice during each session.

IV. Training for Field Center CT Technologists

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V. Participant Scheduling

The MESA operations committee will arrange details of scheduling. Each scanning site will provide their local Field Center with the days/times when MESA participants may be scheduled and the Field Center will contact participants to arranging their appointments for their CT scan. Whether certain days/times will be held for MESA participants only, until 2 weeks or a certain amount of time prior to the day of the appointment, will be agreed upon between the scanning center and Field Center. A Field Center interviewer/scheduler will be responsible for explaining and obtaining consent for the CT examination. Participants will be scheduled for a certain date and time, and transportation arrangements, if necessary, will be arranged by the Field Center interviewer/scheduler. A confirmation appointment letter will be sent, providing the time, date, and directions to the scanning center, and describing the procedure.

VI. Scanning Table and Calibration Phantom.

A special gel stuffed mat will be provided with the calibration pad phantom to prevent artifacts and for subject comfort. This pad is placed between the phantom and the patient. The calibration phantom will be placed inside the blue catcher bag with its long axis parallel to the long axis of the scanning table. The phantom is made of tissue equivalent plastic with rods of hydroxyapatite of known radiographic density. The technologist will position the subject so that the length of the phantom covers the expected length of the heart. The phantom will be the one pictured



on the right.

VII. Scanning Procedure

The scanning procedure described below, **consisting of two scans done in succession on each subject**, will require approximately 20 minutes of the subject's time. Minimal respiratory motion and maximum accuracy and reproducibility require this duration. In unusual cases, this may require as many as 30 minutes. In many cases, the procedure will be completed in 15 minutes or less.

Entering the MESA ID and ACROSTIC

This very important step must be done correctly to prevent any irretrievable loss of CT data. All necessary information needs to be entered into the system, including your technician ID number, Field Center identification. The MESA seven digit ID number must be placed in the ID Field, and an acrostic defined below will be placed in the name field. The acrostic will consist of the first four letters of the last name followed by the first two letters of the first name and one letter for the gender. Each will be preceded by the letters "MESA".

Example:

ID: MESA1212345 NAME: MESADETRROM

The time stamp on each CT record will determine whether the scan is the first or second in the sequence of two scans.

Preparation of the Subject (3 minutes). Subjects weighing more than 300 pounds will not be scanned due to technical difficulties. The technologist will ask women if they might be pregnant and will not scan them if they answer affirmatively. The technologist will attach three electrocardiographic electrodes under the left clavicle and on either side of the thorax near the axillae (to maximize ECG signal). The technologist will ask each subject for their self reported weight in pounds and will use this value to decide if the subject satisfies the "Large Patient" criterion.

Breath Holding Instruction (3 minutes). The technologist will instruct the subject on the importance of breath holding and immobility during scanning. An interpreter will assist in the instruction of subjects, not fluent in English. All centers will have access to interpreters fluent in languages spoken by at least 95 percent of potential volunteers. Our preliminary study suggests that at least 99.5% will be able to hold their breaths for more than 15 seconds and 80% will be able to hold their breaths for more than thirty seconds. Only after the technologist is satisfied that the subject understands the importance of breath holding, will he/she proceed.

Checking the Scout Image (1 minute). The technologist will instruct the subject to take three deep breaths, and then to hold his/her breath (at end-inspiration), while acquiring an 11 cm scout image, beginning 180 mm below the sternal notch. This will provide views of the chest on the image monitor at the operator console. From this, the technologist will check patient centering and choose the position for the highest scan (at the lower margin of the

bifurcation of the main pulmonary artery). The couch will be moved to the start position. The technologist will check subject and phantom positioning in the scout image.

Default Scanner Settings. At least 10.5 cm of data in the z direction will be acquired with each scan and the scan Field of View will be 35 cm for all scanners (to incorporate the phantom in the image). For each scanner, the default settings will be as follows:

- **GE Light Speed (800msec rotation time) - 120 kVp, 200 mA, .8 sec scan, 4 x 2.5mm collimation, sequential axial scans, segmented reconstruction, standard filter.**
- **GE Light Speed (500msec rotation time) - 120 kVp, 320 mA, .5 sec scan, 4 x 2.5mm collimation, sequential axial scans, segmented reconstruction, standard filter.**
- **Siemens Volume Zoom - 140 kVp, 139 mA, .361 sec scan, 4 x 2.5 mm collimation, sequential axial scans with prospective cardiac gating, standard filter reconstruction (as designated on the VZ). Note, set mAs at 50.**
- **Imatron EBCT scanners: 130 kVp, 630 mA, scan time 100 msec, 3mm collimation, sharp reconstruction filter. For EBCT scans, prospective cardiac gating will be used with scanner triggering at 80% of the electrocardiographic RR interval. The EBCT scanner table will pause after each table increment of 3 mm (sequential axial scans) . The technologist will acquire 35 to 40 image slices as needed to ensure that the entire heart is scanned**

Large Patient Scanner Settings

For the helical (non Imatron) scanners *only*, the mA will be adjusted upwards for larger patients. For patients > 220 lbs, the mA will be increased by 25%. Specifically:

- **For General Electric LightSpeed scanner (800msec rotation time): increase to 250 mA. All other parameters are to remain the same.**
- **For General Electric LightSpeed scanner (500msec rotation time): increase to 400 mA. All other parameters are to remain the same.**
- **For Siemens Volume Zoom scanners: increase to 174 mA. All other parameters are to remain the same. Note, increase mAs to 63.**

Reconstruction The technologist will use the 35 cm field of view and the sharp reconstruction kernel for all EBCT scans and 35 cm field of view and the standard kernel for all other scans.

Imaging (6 minutes). All scanning will be done with a single breath hold. The Siemens Volume Zoom helical scan acquisition requires a breath hold for the participant ranging from 15 to 25 seconds depending upon the combination of heart rate and heart length. EBCT and General Electric scan acquisition requires a breath hold of between 25 and 40 seconds depending on the same factors. The technologist will always ask the subject to take two deep breaths and then a third before imaging commences.

Though total imaging time will be approximately 30 to 40 seconds, double scanning will require about 5 to 7 minutes to complete. The technologist will first acquire one entire

series of image slices. The technologist will instruct the subject to relax on the table while he/she reconstructs and assesses the adequacy of positioning, ECG gating and lack of respiratory motion. If these are adequate, the technologist will immediately acquire another series of image slices while the subject remains immobile and in an identical position. Once again, he will assess the adequacy of the images.

Radiation Dose Considerations. The radiation dose during one set of scans is approximately 600 to 800 mrem (skin dose) for all scanners used in this protocol. This will be applied to the thorax covering from 10.5 to 12 cm in the z axis. This would have to be multiplied times the number of scans (2).

The following may be helpful for informing subjects and institutional review board regarding radiation exposure from this study.

Scanner	Skin Dose	Effective Dose	Background Effective
Imatron	1260 mrem	2.0 mSv	2.3 – 3.0 mSv
Siemens	1900 mrem	3.0 mSv	2.3 – 3.0 mSv
GE	1540 mrem	2.4 mSv	2.3 – 3.0 mSv

Current estimates of the risk of fatal cancer from ionizing radiation for the adult working population are .004% per mSv (effective dose) over a 20 year period (assuming linear extrapolation). Thus, the additional risk of developing cancer for a participant in MESA during the next twenty years is between 8 per 100,000 and 12 per 100,000 for each CT examination. Each CT examination adds the equivalent risk of one year of background ionizing radiation.

Ref: International Commission on Radiological Protection. "1990 Recommendations of the International Commission on Radiological Protection", ICRP Publication 60, Ann ICRP 21(1-3), 1991.

Identification, Storage and Transport of Image Data. The following will ensure proper scan identification and subject confidentiality. The technologist will record each volunteer's study id number in the medical record number field of each scan. A five character acrostic consisting of the subject's first, middle and last initials and a digit for the field site will be put in the last name field of the header. The date and times of the two scans and the identity of the scanning site and technologist will be identified in the appropriate fields. The technologist will store images in retrievable format on optical disk (MODs). Images will be transferred to a local work station which has an INTERNET interface to be used for transfer to the reading center.

VIII. Scanner Quality Assurance

Regular Scanner Calibration to Water. It is strongly recommended that the technologist at each center check the scanner at least weekly using a standard water phantom. These will include zeroing and calibrating the scanner unit.

Twice a Month CT Calibration Measurements for Quality Assurance.

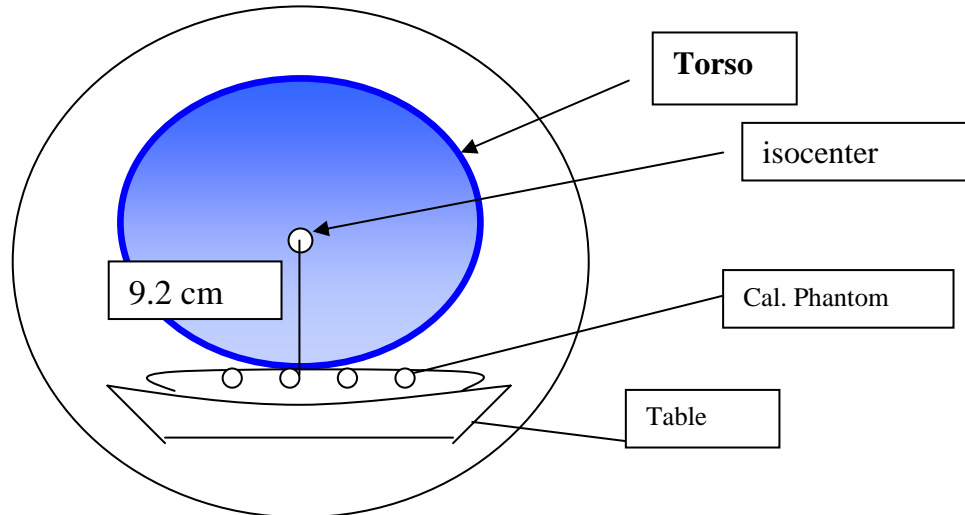
Each clinical site will have a QCT calibration phantom (Image Analysis Inc) and a torso QA phantom (Image Analysis Inc) containing a central plug with a known concentration of hydroxyapatite (100mg/cc). The calibration pad contains cylindrical rods and will be contained inside of a recess in the table pad for patient comfort.

Every two weeks, quality assurance scans of the torso phantom allow convenient and quick verification of accuracy and precision of the CT scanners at different sites.

Quality assurance calibration measurements will be done weekly during the period of the pilot test study and then twice a month during the active scanning period of the study.

Positioning the Calibration and Torso Phantoms.

Make the table height such that the center of the calibration phantom is located at a distance of 9.2 cm +/- 1.0 cm from isocenter of the scanner field of view. Place the torso phantom on top of the calibration phantom (positioned in couch pad) and using your laser alignment light, adjust the table height until the torso center insert is at the location of isocenter (on grid). This is the table height you will use for QA scans with your Torso phantom.



Scanning the TORSO QA Phantom

After the correct position has been determined, take a vertical axial slice through the center of the TORSO phantom. Use the same parameters as with patient exams. With helical scanners, you should acquire two centimeters of volume data including the center of the torso phantom. Use the same scanning parameters as are used during the

study. Reconstruction should be done with the same parameters as in scanning study subjects.

Then display your axial image on your CT monitor and examine it to ensure that it is free of artifacts, such as air gaps and streaks. Ensure that the calibration phantom is included in the field of view. If there are significant artifacts over the calibration phantom, you should discard the image and rescan the phantom.

Using your CT software place ROI's on the calibration phantom reference samples (0, 50, 100, 200 mg/cc). The 0 sample will be an apparent blank space on one end of the calibration phantom. Then place an ROI in the TORSO vertebral sample. The ROIs should be as large as practical while remaining completely within the reference cylinder. (We recommend ROIs about 70% of the sample area.) Record the five mean CT numbers within these five ROIs and send these numbers by FAX or E-mail to the MESA reading center (Email, fax) using the standard QA forms provided (attached QA Data Sheet). Record the five mean CT numbers within these five ROIs.

File the data sheet for your records.

Send these forms by FAX to the study reading center.

Instructions to the Reading Center.

Use the QCT software available to the reading center that runs on a standard PC using Windows 95. Click on the QXCT-3000 icon on your desktop. Click the enter QA button on the toolbar. A QA data entry screen pops up. Enter the data from the QA data sheets from the field centers. When all the data is entered, click OK. This will save the data to the QA database and open a window showing the QA report. To discard the entries you have made, click cancel.

The QCT 3000 software computes the calibrated calcium density for the Torso phantom. The results are displayed in graphic and tabular format. The software also accesses the database and retrieves any previous data on the Torso phantom. Previous data and calculated changes are displayed in the tabular form.

The individual QA torso readings should be maintained at within $\pm 3\%$ of the mean value of all the reading. If the values fall out of range, the field site must be notified in order to have the scanner checked by the field engineers.

The QA report has three major parts:

- a) Phantom and Scanner Information. This includes the phantom type and the exam number, the details of the CT scanner and technique.

Click the image of the phantom which matches the one used at the field site and enter the serial number of the phantom.

- b) QA Readings, together with past readings are plotted in graphical format. The graph is color coded and includes a band that covers the mean $\pm 3\%$.
- c) The QA readings are also printed in tabular form by date. The change in the reading is also tabulated. Also shown is the mean and standard deviation of all the readings.

Some common sources that cause poor results include, inappropriate table height (TORSO plug should be at isocenter when scanned), mispositioning of the phantom, old or improper CT calibrations, or use of improper scan parameters.

Given there are multiple technicians at each field center, on a quarterly basis, interscan percent variability by the reading center will be calculated for each technician, obtaining the mean percent difference in scores between all duplicate scans performed by a given technician. Where unacceptable variability exists within a given technician (greater than two standard deviations beyond the mean variability for a given center), the reading center will advise the field site and an investigation into the reasons for this and further training / recertification, as needed, will be done.

IX. Alerts

Communication with Field Center by Reading Center

The Reading Center will review all scans within two weeks and will indicate any alerts. A cardiologist or radiologist investigator will review all scans and will identify eventual alerts. The investigator will telephone the CT investigator at the field site and the coordinating center and will write a letter (see Attachment) with copies to both. Pathological findings constituting alerts will include pulmonary infiltrates, pericardial or pleural effusions, tumors, dilatation of the aorta greater than 4 cm and pathological rib fractures.

X. Data Transmission of Studies

The technologist will transmit the studies to the local work stations if this has not been done during scanning. He/she will archive each study locally and leave a copy on the hard disk of the work station until it has been successfully transferred to the reading center. He/she will transmit the studies electronically using DICOM transfer on the local workstation to the reading center on a given afternoon of each week. He will simultaneously FAX the list of MESA ID numbers and acrostics transmitted at that time to the FAX number **[Removed for LAD release]**.

The CT Data Manager will check each study to ascertain if it has been completely received. If it has been so received, the study will be put on the queue to be read by the reader. If it has not been received, the data manager will immediately communicate the identity of the study to the field site technologist and request that another attempt be

made to send that study. The CT data manager will enter the identity, scan date, scan time and date and time of transfer of each study into a running log, a copy of which will be sent weekly to the coordinating center.

The CT reader will backup studies onto CDs as they are read. The reader will label each disc with a volume name and the date the CD was created. The reader will print a directory to be stored with each CD. Each CD-R that is archived will thus have a printed list of its contents inserted into its sleeve. The Data Manager will back check the CDs to be sure that they contain complete studies.